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DISCUSSION

JOHN C. JONES, M. D. (427 South Arden Boulevard, Los Angeles).—As the result of the increased and discrete employment of the bronchoscope in cases of tuberculosis of lungs with tracheobronchial symptoms, many heretofore unexplained clinical and roentgen "mysteries" have been solved. This has been accomplished without great sacrifice and discomfort to the patient, without major complications, and has led to a considerable number of patients being spared major surgery when the latter would have been fatal or at least carried a high morbidity. At the same time local treatment of these lesions through the bronchoscope will result in the arrest of tuberculous disease in a certain number of cases where persistent positive sputum alone holds the patient bedfast a long time in spite of a roentgenogram which failed to show parenchymal activity.

Of all these cases of tuberculous tracheobronchitis, probably those of a stenosing character, with tuberculous bronchiectasis and severe secondary infection distal to the stenosis, carry the gravest prognosis by virtue of their poor bronchial drainage and its inevitable severe toxicity. Collapse therapy fails to alleviate the burden of this toxicity, and may only increase it if the drainage is further hampered by "bronchial kinking." The ideal treatment is eradication of the disease by lobectomy or pneumonectomy, depending on the location and extent of the disease.

About one year ago we had a 28-year-old female with tuberculous bronchiectasis of the entire left lung as the result of a tuberculous ulcerating stenosis of the left main stem bronchus. Her temperature had been elevated to 102 and 103 degrees Fahrenheit persistently for two and one-half years, during which time bed rest, pneumothorax, and phrenicectomy had failed to relieve her symptoms. She had lost forty pounds in weight and had continued a downhill course throughout her sanatorium treatment. A total left pneumonectomy with drainage was completed eleven months ago and the patient had an uneventful surgical postoperative course. In three months she regained all her lost weight and was without fever and sputum, but a fistulous tract persisted in the chest wall when she was discharged from the hospital four months postoperatively. Unfortunately, following two months of too active life on the outside, she returned with an exudative contralateral spread which has shown a progressive clearing without excavation on return to bed rest in the hospital.



SIDNEY J. SHIPMAN, M. D. (490 Post Street, San Francisco).—Doctors Pierson and Samson's discussion of tuberculous tracheobronchitis is very timely indeed. The entire subject is a new one, for although the effects of this disease have been observed for many years, the significance of the condition has remained almost completely unrecognized.

Tuberculous patients who have been doing well but who suddenly begin to wheeze, particularly if this wheezing is localized to the affected lobe or lung, should be suspected of having tuberculous bronchitis. Whether general or local treatment is advisable depends upon the individual case. Tuttle of Detroit recommends 35 per cent silver nitrate applied locally through the bronchoscope. I, personally, prefer general irradiation with the quartz lamp to the point of tanning, particularly in the early, allergic reactions which it is so important to recognize. Probably this form of treatment is less and less effective as time goes on, until, of course, it has no effect at all on the scarred stenoses.

The relationship of the condition to "tennis-ball cavities" is interesting, as the authors have pointed out. It is well recognized now that not all cavities are the result of the expectoration of caseous material, but that they develop as the result of the valve effect due to diseased bronchi. The lumen of the bronchus is diminished, the bronchus expands during inspiration, allowing air to enter the lung, but contracts on expiration and does not permit it to get out. Apparently this mechanism keeps cavities blown up or prevents their collapse. Theoretically, a return of the bronchus to normal should eliminate this mechanism, although certain writers, notably Coryllos, have contended that it would be better to have the condition go on to complete closure of the bronchus, when absorption of the air and closure of the cavity should take place. Whether either or both of these ideas are correct, time will tell.

Meanwhile the subject is a fascinating one for investigation, and it is to be hoped that Pierson and Samson will continue the work which they have so well described.

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## ROENTGEN TREATMENT OF CERTAIN HEMORRHAGIC DISORDERS*

*By* L. H. GARLAND, M.D.
*San Francisco*

DISCUSSION *by R. S. Stone, M. D., San Francisco; John C. Ruddock, M. D., Los Angeles; S. P. Lucia, M. D., San Francisco.*

FOUR years after Frank's[5] description of thrombocytopenic purpura as a separate entity, in 1920, Stephan[17] reported two cases as cured, following roentgen irradiation to the spleen. Since that time there have been many reports of single cases or small series of cases treated by irradiation, some with favorable results and some unfavorable. Doubtless, among the reasons for the variability in results is the variability in severity of individual cases of thrombocytopenic purpura hemorrhagica; another reason is the variable and, in some cases, the incomplete nature of the roentgen therapy given. With more careful classification and selection of cases, and with irradiation, especially of cases of splenic thrombocytopenic purpura hemorrhagica, results appear to be much more encouraging.

### IN THROMBOCYTOPENIC PURPURA

Mettier and Stone[10] treated six patients with essential thrombocytopenic purpura by fairly large doses of roentgen rays to the spleen, and secured remissions lasting up to four years. Four of the cases were acute, and two of the cases chronic. Most of the patients received 200 r daily or every second day to the spleen, using fields approximately 10 by 15 centimeters (200 KV, filter equivalent to 1.00 millimeter of copper). A total of from six to twelve treatments was given to most of the cases. All of the patients showed remarkable increases in platelet counts immediately or soon after irradiation, the rise being approximately 500 per cent. Following the platelet response, the clotting mechanism gradually became normal and the bleeding gradually lessened. In the chronic cases the plate-

*Roentgen treatment of the spleen, to shorten bleeding time in thrombocytopenic purpura and in postoperative capillary hemorrhage.

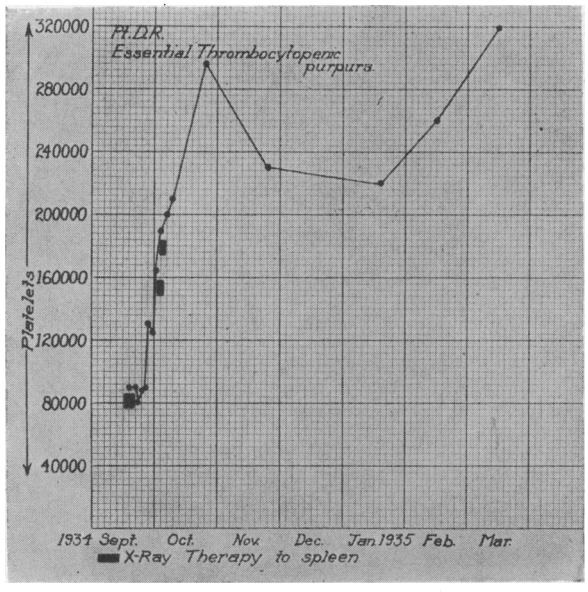


Fig. 1.—Chart illustrating increase in blood platelets, following roentgen irradiation of spleen—in case of essential thrombocytopenia. (Figures 1 to 4 are by kind courtesy of Doctors Mettier and Stone.)

lets dropped again soon after treatment was discontinued, but apparently without associated bleeding. One case of acute fulminating purpura resisted all treatment. In summary, five of six cases did well, but one patient with acute fulminating purpura died.

Rudisill[14] treated eight cases of thrombocytopenia (four purpuric and four nonpurpuric) with a somewhat similar technique, 200 r to the spleen, repeated from one to six times (200 KV, filter equivalent to 0.5 millimeter of copper, field 20 centimeters in diameter). He "found roentgen treatment so satisfactory that it is impossible to understand why it has not come to be considered practically a specific therapeutic agent in primary thrombopenia with hemorrhage." Seven of the cases showed complete remissions, lasting from one to four years, the average being over two years. One patient, a boy of eight, complicated by acute myelogenous leukemia, died of the leukemia.

Marzullo[9] reported four cases of thrombocytopenic purpura treated by x-rays, two of which patients improved but recurred, two died, one over a year after treatment. In this case, bleeding time fell from twelve to two and one-half minutes following treatment.

*Results of Splenectomy.*—In contrast with the above results from roentgen therapy, it is well to compare the results of splenectomy. Brown and Elliott[8] reported twenty-one cases of thrombocytopenic purpura hemorrhagica; ten were treated by splenectomy (one mild case, six moderate, and three severe cases) in eight of whom excellent remissions were secured; one of the patients improved and one died. The average duration of the remissions was over five years, varying from one to eleven years. The other eleven cases were not operated on; five improved, five remained unimproved, and one died. None was treated by splenic irradiation.

Marzullo[9] reported nine cases treated by splenectomy, five of whom recovered, two recurred, and two died.

Mettier,[11] commenting on splenectomy, observes that "removal of the spleen is not entirely satisfactory; the mortality rate is high and a high percentage of patients have recurrence of symptoms."

### RATIONALE OF TREATMENT

The exact reason for improvement in purpura hemorrhagica following splenic irradiation is not known. It is quite definite that irradiation is followed by an increase in blood platelets, diminution in bleeding time,† and coincident diminution or disappearance in hemorrhagic tendency. Rudisill believes that there may be two distinct classes of essential thrombocytopenic purpura; one secondary to toxemia and one secondary to unknown causes. In the former class, "the spleen's function" of platelet destruction "need only be lowered, until the toxemia is overcome" (usually accomplished by one to three roentgen treatments), but in the latter case "it may be necessary to render the spleen permanently functionless by intensive irradiation." (The question of this so-called roentgen-ray "splenectomy" is also discussed by Mettier and Stone.[10]) Lucia[7] observes that "exposures to x-ray alter the plasma in such a way as to inhibit bleeding."

### ROENTGEN THERAPY FOR CAPILLARY OOZING AND INCREASED COAGULATION TIME

There is very little literature on the control of increased coagulation time and capillary oozing by roentgen irradiation of the spleen, except incidental to that already referred to above in connection with the treatment of purpura hemorrhagica. Markovits[8] refers to work by Tichy and Nigst, but does not give any specific references. With Dr. Roy Parkinson we recently studied the effect of roentgen irradiation of the spleen in "normal" persons—mostly patients admitted to the hospital‡ for minor surgery; sixty-one patients were given a single dose of 160 r to the spleen and forty-eight patients were untreated.[18] The investigation was conducted as follows: a platelet count and coagulation time was determined at 7:30 a. m. The

†Note on coagulation and bleeding time:

Coagulation time: The coagulation time is the time which the blood takes to clot after it has been shed. As determined by different methods, it varies considerably, since the criterion of clotting is not the same in all. On this account the values are not absolute, and the results obtained by different methods cannot be compared strictly with one another. A simple method is to draw a drop of blood into a capillary glass tube about 10 cm. long, and break off a section from time to time until fine threads of fibrin appear between the ends of the broken sections; the time elapsing from making the wound to the time of fibrin development is the coagulation time (about four minutes being normal).

Bleeding time: The bleeding time is the time a drop of blood (produced by pricking the skin) takes to clot sufficiently to close the puncture and stop the bleeding. It is determined by pricking the skin and touching the wound every few seconds with a piece of filter paper, the moment when the latter ceases to be stained being the end-point (normally about three minutes). The coagulation time is a better gauge of the body's ability to protect itself against hemorrhage than the bleeding time.

In hemophilia the coagulation time is greatly prolonged, but not the bleeding time; the platelets are not decreased in number, but show lessened fragility; the clot usually retracts normally. In purpura hemorrhagica thrombocytopenica the coagulation time is usually within normal limits, but the bleeding time is prolonged; the platelets are decreased in number; the clot does not retract normally and is soft and friable.

‡St. Joseph's Hospital, San Francisco.

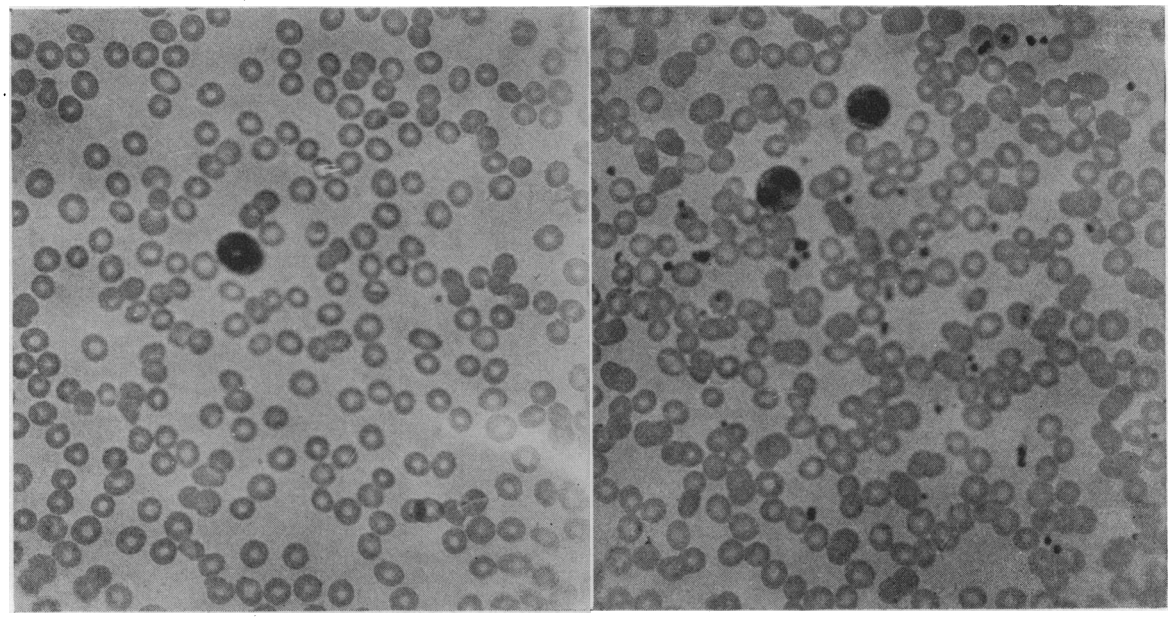

Fig. 2 Fig. 3

Fig. 2.—Blood smear showing absence of platelets in patient with essential thrombocytopenic purpura.
Fig. 3.—Blood smear showing presence of large number of platelets in same patient as Fig. 2, following splenic irradiation.

treated cases were then given a dose of 160 r to the spleen. In a number of cases, a platelet count and coagulation time was done immediately after finishing treatment, and in all cases was done at 4 p. m. The surgical procedure was done at approximately 8 a. m. Similarly, in the control cases, platelet counts and coagulation times were determined at 7:30 a. m. and 4 p. m., and similar surgical procedures were performed at 8 a. m.

In fifty-nine of the sixty-one cases treated by x-rays there was a drop in coagulation time averaging 2.5 minutes, and an increase in platelet count of from five- to sevenfold. The most significant drops in coagulation time were in those cases in which the coagulation time taken before irradiation (that is, patient's "normal" coagulation time) was six minutes or more. For example, in a group of fifteen patients with coagulation time exceeding six minutes, the average time before irradiation was 7 minutes 41 seconds, and after irradiation 3 minutes 42 seconds. The change took place immediately. The surgeon often observed that the operative field was strikingly dry—so remarkably so that, for example, in tonsillectomy cases he was able to tell whether the patient had or had not received irradiation by the amount of capillary oozing.

In the forty-eight control cases there was an average drop in the coagulation time of a little less than half a minute, attributed presumably to the surgical procedure or the anesthesia.

Coagulation times were done by the capillary method, using one millimeter diameter tubes and taking blood from the ear. The platelet counts were done by the chamber method, using Wyckoff's modified platelet stain. Doctor Downey kindly supervised this part of the work, using different laboratory workers and internes from time to time in order to avoid bias. The x-ray factors used were 130 KVP, filter of 0.25 millimeter copper, 25 centimeters target-skin distance, 13 centimeters diameter skin area, single dose of 160 r (measured in air, without backscatter).

## RATIONALE OF TREATMENT

Markovits[8] believes that roentgen irradiation causes "disintegration of leukocytes and lymphocytes in the spleen, with consequent liberation of a ferment which promotes coagulation." However, other authors (Nigst, Szenes, Gal, Amreich[8]) allege that acceleration of blood coagulation also occurs following irradiation of other organs, such as the liver, lung, and parotid. Arkussky[1] reports decrease in iron excretion following irradiation of rabbits' spleens, with associated storage of iron in the liver. Bourne[2] reports that there is a significant drop in the polymorphonuclear leukocytes in the spleen following irradiation. However, we do not know whether it is a splenic or "total blood stream" effect. Sokolov[16] has shown that irradiation affects certain mineral constituents of the blood plasma, producing physiochemical changes that affect the general organism.

## INDICATIONS FOR SPLENIC IRRADIATION IN HEMORRHAGIC DISORDERS OTHER THAN PURPURA

From the above observations it is obvious that splenic irradiation is of considerable value as a preoperative measure in patients with low platelet counts or increased coagulation times. It is also of value in some benign uterine hemorrhages. Volpe[18] reports a series of cases of metrorrhagia in young women, apparently cured by doses of 200 r to the spleen repeated after five days, and again at monthly intervals for from two to six treatments. Markovits[8] suggests its use also in melena neonatorum, hemophilia, and chlorosis. We have not used it in any of these kinds of cases, but

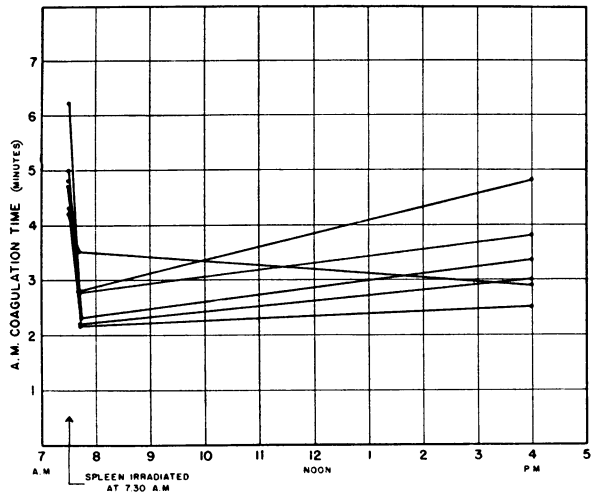


Fig. 4

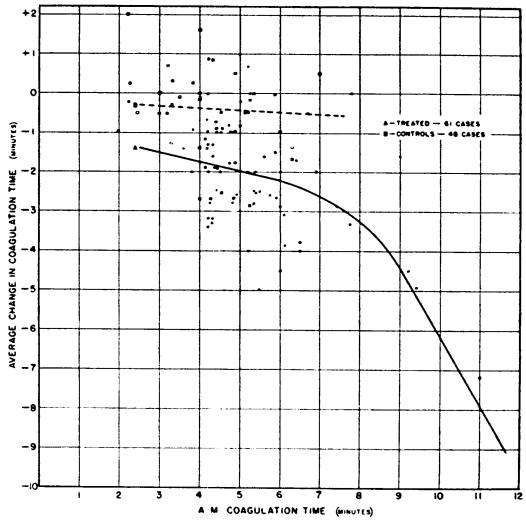


Fig. 5

Fig. 4.—Chart showing shortening of coagulation time immediately, and for twelve hours following splenic irradiation (six cases).

Fig. 5.—Chart showing shortening of coagulation time eight hours after splenic irradiation (sixty-one cases) with controls (forty-eight cases).

see no reason why it should not be tried following or in conjunction with the use of the more time-honored and simpler remedies. It may also be valuable in epistaxis, gastric oozing, and in other types of bleeding.

## SUMMARY

Moderate or large doses of x-rays administered to the spleen control or produce long remissions in many cases of essential thrombocytopenic purpura hemorrhagica. A sufficient number of years has not yet elapsed to warrant the conclusion that the treatment is superior to splenectomy, but recent reports suggest that it is at least equally effective as such, with, of course, a zero mortality from the treatment itself. In cases in which it is proposed to attempt ablation of splenic function by irradiation it would be advisable to check the accuracy of the roentgen beam centering by means of a film, since the spleen is variable in position and it is obviously important to be certain that the entire organ is being irradiated.

Small doses of x-ray administered over the spleen of a patient with increased coagulation time produce rapid decrease in coagulation time, with associated rise in platelets and consequent control of capillary hemorrhage. The treatment causes no inconvenience to the patient and may, indeed, be done en route to the operating room, or, with a bedside unit, in the case of those gravely ill. Irradiation is simple, rapid and effective in a high percentage of cases.

450 Sutter Street.

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## DISCUSSION

R. S. Stone, M.D. (University of California Hospital, San Francisco).—Doctor Garland was kind enough to refer, in his discussion, to the paper by Doctor Mettier and myself on the irradiation treatment of patients with essential thrombocytopenic purpura hemorrhagica. In connection with the work which Doctor Mettier and I reported, I can only add that we are still as satisfied with the method of treatment as we were when the report was made, and that patients there reported are continuing to do well. The administration of further x-ray therapy to these patients has been extremely rare.

In a recent issue of the *Journal of the American Medical Association* there was an article by Doctor Wintrobe on

purpura hemorrhagica, and in it x-ray therapy was given extremely small mention. I think that this is evidence of the fact that the irradiation treatment of the spleen for purpuric conditions is not sufficiently well understood or appreciated. This is most likely due to the fact that the amount of irradiation given in the majority of instances is not sufficient to accomplish the results desired. If only one or two treatments are given to the spleen, there may be a temporary increase in the platelet count, and a cessation of hemorrhage; but if the treatment is not carried to a much higher level the platelets are likely to drop again and the condition recur. We have found it necessary to carry the treatments to as much as 1,200 roentgens to the spleen from at least two ports in order to make the cure more or less permanent.

I have not had the opportunity to check or repeat the work which Doctor Garland has done in connection with roentgen therapy for capillary oozing and increased coagulation time. I am extremely interested in this work, and it opens up a new field. If the preoperative irradiation of patients whose coagulation time is prolonged were established as a routine, it seems likely that the marked bleeding of these cases would be a thing of the past. From Doctor Garland's report it would seem that this would be a logical step, particularly in the case of tonsillectomy operations. I hope that this work of x-ray treatment of the spleen will receive a more widespread attention, and be given a more thorough trial in the future, so that either corroboration or disproval of the results which he has reported, and those which Doctor Mettier and I reported at an earlier time, may become established.

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JOHN C. RUDDOCK, M.D. (1930 Wilshire Boulevard, Los Angeles).—The subject of the treatment of thrombocytopenic purpura hemorrhagica is one that has been before the medical profession since 1925, at the time Pancoast, Pendergrass, and Fitzhugh published "The Status of Roentgen-Ray Treatment by Irradiation of the Spleen." Controversy between surgeons and roentgenologists has been evident as to which is the best method of treatment.

The roentgenologists certainly can say that there is a zero mortality from the treatment itself. The surgeons state that, by the complete removal of the spleen, they reduce the possibility of remissions. It is a question whether complete ablation of the spleen can be done by roentgen-ray without other effects upon the body than the purpose for which the splenectomy was done.

Cases are often encountered of thrombocytopenic purpura, with active bleeding, in which the patient is practically "bled out," and in spite of transfusions it is impossible for them to retain enough blood to build them up. X-ray therapy is slow, but I must say that it is safe at this stage. Often we must give repeated transfusions during the irradiation of the spleen, as the bleeding does not stop immediately, but may continue for a number of days before clotting and bleeding time approach normal. It is my opinion that when this has been accomplished, and by means of transfusions the blood volume has been returned to normal, that a splenectomy should be done. It is my opinion, also, that remissions, if these patients were treated by a combination of roentgen-ray and surgery, would be fewer and the surgical risks would be lessened if the patients received irradiation in order that they may be made a good risk.

The irradiation of the spleen in normal persons prior to minor surgery in order to guard against capillary oozing and postsurgical hemorrhage is excellent, and I believe it is a timely subject.

Doctor Garland should be complimented on his excellent review on the subject of this type of disease treatment, and on his calling attention to the fact that, due to the variability and severity of individual cases and variability of the nature of the roentgen therapy given, much variability will be noted in the results reported from the treatment of this disorder both by roentgenologists and surgeons.

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S. P. LUCIA, M.D. (2529 Union Street, San Francisco). Variation in the results of roentgen irradiation of the spleen in thrombocytopenic purpura hemorrhagica is a matter not only of variability in the severity of individual cases, and in some instances of inadequacy of amount of roentgen therapy, but also of variability in the type of the disease. Thrombocytopenic purpura is usually a symptom-complex of a more complicated disease involving alterations in structure of the hematopoietic tissues and blood plasma, and in permeability of capillaries. It may be a manifestation of infections, leukemia, heavy metal therapy, or arteriosclerosis. A variety of this condition, occasionally congenital, is seen in women who suffer from endocrine glandular hypofunction. All types of purpura may or may not be associated with splenomegaly.

The purpuric state is not necessarily associated with thrombocytopenia—in fact the blood platelets may be found to be increased in numbers. Frequently it is difficult to state which factor—platelets, plasma, or capillaries—is most important in a given case. One thing is certain: that in order that purpura may occur, the capillaries must be abnormally permeable. It is indeed unfortunate that the varieties of thrombocytopenic purpura cannot always be differentiated or the mechanism of their production be understood. This, I believe, is the reason for discord in the reports of the results of treatment found in the literature.

Before the treatment of thrombocytopenic purpura hemorrhagica can be placed on a rational basis, more careful study must be made of plasma, capillaries, and platelets in individual cases. It is important also to learn the mechanism by which blood platelets are increased and the manner in which the coagulation of blood is altered after exposure to roentgen irradiation.

In conclusion, it may be stated that: (1) Acute purpura without splenomegaly is best treated by transfusion. This variety frequently proves refractive to all therapeutic measures, including roentgen irradiation and splenectomy. (2) Chronic purpura without splenomegaly (refractive to medical treatment) may react favorably to roentgen irradiation for limited periods of time. (3) Acute purpura with splenomegaly (usually secondary to some more complex disease) frequently gives a favorable response temporarily to a variety of therapeutic measures, including roentgen irradiation. (4) Chronic purpura with splenomegaly usually responds satisfactorily to roentgen irradiation.

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## VITAMIN D IN ACNE*

### A COMPARISON WITH X-RAY TREATMENT

*By* MERLIN T.-R. MAYNARD, M.D.
*San Jose*

DISCUSSION *by George V. Kulchar, M.D. San Francisco; Henry J. Templeton, M.D., Oakland; Nelson Paul Anderson, M.D., Los Angeles.*

THERE is probably no skin disease of greater importance to the human race than acne. It is undoubtedly our commonest skin disease, and it is rare that any individual reaches maturity without having had it in one of its phases. It is a disease of considerable economic importance, as the disfiguring scars of a severe case are never completely obliterated. It is also a disease of youth. It attains its most noxious form at the time the individual first has to earn his own living. It is undoubtedly responsible for many failures in getting business positions. It is also the basis for inferiority complexes and discouragement in young people.

The dermatologist sees only a small percentage of patients, since many patients are not treated in the expectancy of the condition being outgrown. A goodly percentage are treated over the drug counter or by the family doctor, usually with little success. In dermatological practice, acne cases are likely to rank about third in the frequency of skin diseases, and for this reason are of considerable

* Read before the Dermatology and Syphilology Section of the California Medical Association at the sixty-sixth annual session, Del Monte, May 2–6, 1937.